UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/090,983	03/04/2002	William C. Manning JR.	20263.50	7567

7590 08/13/2003

CHIRON CORPORATION
Intellectual Property - R 440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/090,983	Applicant(s) MANNING ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-44* is/are pending in the application.

4a) Of the above claim(s) *35 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-34,36-40 and 42-44* is/are rejected.

7)☒ Claim(s) *30-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

Election/Restrictions

Applicant's election of Group II, claims 30-34, 36-40 and 42-44, as they relate to gene therapy methods, in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 30-44 are pending, however, claims 35 and 41 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 30-34, 36-40 and 42-44 are under current examination.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **All nucleic acid sequences in the specification require Sequence Identification Numbers. For Example, see page 34, lines 8-9).** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing."

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed

150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The Abstract contains the phrase "such vectors".

The disclosure is objected to because of the following informalities: The sentence on page 57, line 16-17 is incomplete.

Appropriate correction is required.

Claim Objections

Claims 30-34 are objected to because of the following informalities:

The claims encompass transgenic animals as well as animals generated by in vivo gene delivery. Claims should be limited in scope to the elected invention described in the specification, which is a non-human animal model generated by in vivo gene delivery

Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

Claims 30-34, 36-40 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-human animal model of neovascularization comprising a non-human animal having a VEGF transgene administered subretinally using an rAAV gene delivery vector wherein the transgene causes neovascularization, and for a method of using said model for determining the ability of an anti-angiogenic factor to inhibit the onset of neovascularization by co-administration of rAAV vectors encoding VEGF and an anti-

angiogenic factor does not reasonably provide enablement for a non-human animal comprising any angiogenic transgene in the eye wherein the transgene has been introduced through any means to any part of the eye or for a method of determining the ability of an anti-angiogenic factor to inhibit the neovascularization of the eye comprising administering an anti-angiogenic factor to an animal model of neovascularization and determining the ability of said anti-angiogenic agent to inhibit neovascularization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to an animal model comprising a transgene introduced via in vivo gene delivery to the eye (claim 30) wherein the transgene causes neovascularization (claims 31 and 32), wherein the animal is a mouse or rat (claim 33) and wherein the transgene encodes VEGF (claim 34). Claims are also directed to methods of making the animals (36-40) and methods of using the animals to screen anti-angiogenic factors (claims 40-42).

The specification teaches methods to treat, prevent or inhibit disease of the eye by intraocular administration of a gene delivery vector, such as those generated from retroviruses, adenoviruses or adeno-associated viruses, wherein the gene directs the expression of an angiogenic or anti-angiogenic factor (see page 5). The specification further discusses general construction of various gene delivery vectors (pages 13-17) and methods of administering a gene delivery vector to the eye (pages 20-22). More specifically, the specification teaches administering, subretinally to rats, a recombinant adeno-associated virus (rAAV) comprising nucleic acid encoding VEGF operably linked to the CMV promoter (page 56, lines 8-22) wherein the transgene leads to choroidal neovascularization (page 56, lines 20-29) and the use of

said rats as a model to test anti-angiogenic factors for the ability to inhibit neo-vascularization of the eye (page 58, lines 4-23). The specification, however, fails to provide guidance that correlates administration of any angiogenic factors other than VEGF with neovascularization in a non-human animal as encompassed by claims 30-33, 36-39 and 42-44. The specification fails to provide relevant teachings relating to the effectiveness of VEGF in causing neovascularization when administered in any manner other than by subretinal rAAV gene delivery, including intravitreal administration (claim 38) or with use of any other vectors (claims 30-34, 36-40 and 42-44). The specification teaches choroidal neovascularization (pages 56-57) but does not demonstrate that subretinal injection with a rAAV containing a VEGF transgene results in retinal neovascularization (claim 31). Given the lack of guidance provided by the specification, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

1) Claims 30-33 and 36-39 encompass the introduction of <u>any</u> angiogenic transgene to the eye. Claims 36, 39 and 40 encompass delivering the transgene to any part of the eye or to the subretinal space (37) or intravitreal administration (claim 38). The specification is not enabling for an animal model generated by gene-delivery of any angiogenic factor other than VEGF administered using any virus other than an adeno-associated virus wherein the virus is administered to any site other than subretinally.

The specification teaches subretinal injection of an rAAV encoding VEGF. The specification does not teach delivering any gene other than VEGF and does not teach that delivery of VEGF to any site other than the subretinal space leads to the neovascularization phenotype associated with the animal model of the instant invention. The specification does

teach that viral vectors can be administered to other areas of the eye, including intravitreally, however, the specification fails to demonstrate that other sites are effective in generating neovascularization of the retina or choroid as claimed.

The art at the time of filing held that in vivo viral-mediated gene delivery is highly unpredictable. Parameters to consider when making and using a gene delivery vector, include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (Verma, 1997, Nature, Vol. 389, pages 239-242). According to Verma, each gene delivery vector has characteristic limitations and the vector chosen should be done so according to desired parameters such as the temporal length of expression. For example short-term expression can be achieved using adenoviral vectors whereas long-term expression requires stable integration into the genome that cannot be achieved with adenoviral vectors. Eck and Wilson (Goodman and Gilman's The Pharmacological Basis of Therapeutics, 1996, McGraw-Hill, pages 77-101) also support the importance of tailoring a gene therapy vector and methods to specific diseases and disorders (see page 82, column 1, 1st paragraph). For example, Eck and Wilson review the state of the art for gene therapy for inherited disorders and disclose that "the level of protein function necessary to achieve complementation of the defect varies among genetic diseases (see page 78, column 2 , 2nd paragraph). The teachings of Eck and Wilson can be applied to the instant invention. While

the instant invention does not use gene delivery as a means of therapy, it does rely on an effective level of delivery and expression of the gene delivery vector to obtain a desired phenotypic effect.

The art and the specification fail to provide guidance that correlates administration of any angiogenic factor, other than VEGF, with neovascularization when administered via AAV in vivo gene delivery. Due to the unpredictability set forth in the art as described above, it is not clear that this method of administration would actually cause neovascularization of the eye when used with any angiogenic factor other than VEGF. Furthermore, the site of gene delivery is important. The specification teaches that different injection sites results in delivery of AAV to different cell types within the eye. Subretinal injection delivers AAV to the choroidal and inner retinal vasculature while intravitreal injection delivers virus to Muller cells and retinal ganglion cells (page 23, lines 8-15). Accordingly, specification also teaches that subretinal injection of VEGF encoding AAV causes neovascularization of the choroid. The specification, however, does not teach that delivery of VEGF encoding AAV to any site other than the subretinal space will have the intended phenotypic effect, i.e. delivery to the choroid and choroidal neovascularization, or which tissues exhibit neovascularization when VEGF encoded virus is administered in any manner other than subretinally. It is known in the art that it is rare to accomplish transduction of all layers of the retina through intravitreal injection (refer to Ali, Br. J. Ophthalmol., 1997, Vol. 81, pages 795-801, specifically page 797, column 1, 1st full paragraph). Ali also reports that subretinal injection results in poor transduction of photoreceptor cells (page 797, column 1, last paragraph). Thus, tissue and cell infectivity is dependent upon injection site.

Because the specification fails to demonstrate that delivery of a gene encoding VEGF to any area of the eye other than the subretinal space will cause neovascularization, the failure of the specification to teach that any angiogenic factor will cause neovascularization of the eye, and the unpredictability of gene delivery as a means of inducing a specific phenotype, one of skill in the art would not know how to deliver any gene other than VEGF, to any site other than the subretina, using any vector other than a rAAV, such that a model of neovascularization is generated. Therefore, it would require one of skill in the art at the time of filing, undue experimentation to determine how to deliver a gene encoding VEGF to any part of the eye other than the subretinal space to generate a model of neovascularization.

2) Claims 42-44 are directed to a method of using a model of ocular neovascularization to determine the ability of an anti-angiogenic factor to inhibit neovascularization via gene therapy.

The claims encompass the onset of neovascularization as well as ongoing neovascular disease. Although the specification provides an example wherein simultaneous injection of two vectors, one encoding VEGF and another encoding soluble Flt-1 (sFlt-1) or PEDF, prevents neovascularization caused by injection of a vector encoding VEGF alone (page 58), the specification fails to provide teachings or guidance for the breadth of the claimed methods, which encompass testing factors for the inhibition of neovascularization at all stages of the disease. In particular, the specification provides a scenario where the simultaneous injection of vector encoding sFLT-1 with a vector encoding VEGF fails to elicit the neovascularization phenotype expected for injection of VEGF encoded AAV alone. The model never develops neovascular disease prior to Flt-1 vector administration. If the animal never develops neovascularization, then the model is not a representation of neovascularization that can be

inhibited as stated by the claims. The specification provides no teachings or guidance as to how to correlate the results presented in the specification with the inhibition of ongoing neovascular disease in a patient. For example, there are no teachings or guidance provided by the specification with regard to which individuals would be at risk for developing neovascular disease such that the disease could be inhibited prior to onset, or at what stage of onset of neovascular disease the administration of Flt-1 would need to occur to prevent neovascularization. The specific guidance is to inhibiting the onset of neovascular disease by inhibition of angiogenesis prior to the onset of angiogenesis. As such, the example provided by the specification, wherein co-injection of the VEGF and Flt-1 encoding AAV vectors inhibits the formation of neovascular disease of the eye, does not provide correlation with the inhibition of neovascular disease in an individual who has experienced neovascularization. The specification provides no teachings or guidance to show that injection of sFLT-1 vector to a rat model already exhibiting neovascularization would show functional rescue. The specification teaches that inhibition is to result in functional rescue of the eye. However, the model as taught by the specification cannot correlate with functional rescue of the eye, as no eye function is ever lost in the rat. This exemplified inhibition is not representative of inhibition in a patient who develops neovascularization in the eye *de novo*, prior to detection, and the administration of sFLT-1 encoding vector post-neovascularization.

Furthermore, the art of gene therapy, as it pertains to claims 42-44, is highly unpredictable. Romano (Stem Cells, 1999, Vol. 17, pages 191-202) reviews the state of the art of gene therapy noting that although gene therapy has attracted much interest since the first clinical trials, "However, gene delivery systems still need to be optimized in order to achieve effective

therapeutic interventions" (abstract). Romano further state that "Although much effort has been directed in the last decade toward improvement of protocols in human gene therapy, and in spite of many considerable achievements in basic research, the therapeutic applications of a gene transfer technology remains mostly theoretical." (see page 192, column 1, paragraph 3). Romano discusses the importance of tailoring a gene therapy vectors and methods for specific disorders (page 192, column 2, *Gene transfer models*). Romano notes that unpredictable factors such as the particular vector system used as well as the *in vivo* expression of the vector have not been shown to have been overcome by routine experimentation (page 194, column 1).

With particular regard to the instant invention, Ali (Br. J. Ophthalmol., 1997, Vol. 81, pages 795-801) supports the arguments of Romano and states that gene therapy for certain diseases of the eye will be realized sooner than others and in particular, "Gene therapy for inherited retinal degenerations, where there is requirement for long term gene expression with appropriate regulation will present considerable difficulties (page 2, paragraph 1, lines 3-5). Ali teaches the limitations of various retroviral, adenoviral and adeno-associated viruses (page 3, paragraph 2; page 7, paragraph 2). Additionally, Ali concludes that improvements to currently available vector systems are required, as well as increasing the efficiency of transduction of photoreceptor cells and increasing the duration of expression.

The above cited art clearly indicated that at the time of filing the unpredictable state of the gene therapy art in general and, in particular as it related to ocular gene therapy. Although specific vectors, promoters, genes and routes of administration may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels of duration and expression of a

particular gene of interest which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration and therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons discussed in the preceding paragraphs. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in any gene therapy protocols attests to the unpredictable and undeveloped status of the art of gene therapy. The lack of correlative teachings in the art at the time of filing for gene therapy, as a whole, makes it incumbent upon the specification to provide guidance that leads to a therapeutic outcome. In the instant specification, while the subretinal co-administration of rAAV-VEGF and rAAV-sFlt-1 inhibited formation of neovascular disease, there is no correlation between the observed results and the inhibition of neovascular disease by the administration of a gene delivery vector that directs the expression of an anti-angiogenic factor. As discussed previously, the specification only provides support for the co-administration of the described vectors, and further, the specification fails to provide guidance or teachings with regard to which individuals would be at risk of developing neovascular disease of the eye such that one could inhibit formation of the disease.

Note also that the issue of "correlation" is dependent upon the state of the art at the time of the invention. MPEP 2164 discusses that if one skilled in the art cannot readily anticipate the effect of a change within a subject matter to which the claimed invention broadly pertains, the there is a lack of predictability in the art. As the presently claimed subject matter pertains to ocular gene therapy, and with regard to the teachings of Romano and of Ali, it is noted that there

is significant art-recognized unpredictability in ocular gene therapy and the artisan cannot anticipate a therapeutic effect. Thus, what is known in the art provides evidence as to the question of unpredictability.

As such, in light of the state of the art of gene therapy, the specification fails to provide guidance for any of the above parameters for *in vivo* gene expression, and the specification fails to provide clear correlation to carrying out gene therapy with regard to any particular effect by practicing the claimed methods.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of guidance or teaching provided by the specification with regard to inhibition of neovascular disease by administration of an anti-angiogenic factor, as well as the unpredictable and undeveloped state of the art with respect to gene therapy, as well as to the art of gene therapy of the eye, it would have required undue experimentation for one of skill in the art to make and/or use the animal models as broadly claimed.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is incomplete as written. The preamble of the claim is directed to a method for making a non-human model of neovascularization of the eye. However, the claim is incomplete

because the method steps do not relate back to the preamble in a positive process. Appropriate correction is required. Claims 37-40 depend from claim 36.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 31, 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto (American Journal of Pathology, 1997, Vol. 151, pages 281-291).

Claims are drawn to non-human animal model of neovascularization of the eye wherein the animal comprises an angiogenic transgene in the eye (claim 30) wherein neovascularization is in the retina (claim 31) and wherein the animal is a mouse or rat (claim 33) and the angiogenic transgene is VEGF (claim 34).

Okamoto teaches transgenic mice comprising a VEGF transgene operably linked to the bovine rhodopsin promoter (page 282, paragraph bridging columns 1-2) which drives expression of VEGF to the retina, causing neovascularization of the retina (paragraph bridging pages 285-287). A transgenic mouse comprising a VEGF transgene is an animal having an angiogenic transgene in the eye.

Accordingly, Okamoto anticipates claims 30, 31, 33 and 34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36,37,39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okamoto (American Journal of Pathology, 1997, Vol. 151, pages 281-291) taken with Rakoczy, 1999, Drug Development Research, Vol. 46, pages 277-285) and Tomidokoro (1999, Current Eye Research, Vol. 18, pages 381-390).

Claims are directed to methods of making a non-human animal model of ocular neovascularization comprising administering a gene delivery vector which directs expression of an angiogenic transgene (claim 36) wherein the vector is administered subretinally (claim 37) and wherein the vector is rAV or rAAV (claim 39) and wherein the vector encodes VEGF (claim 40).

Okamoto taught making a mouse model of ocular neovascularization by generating transgenic mice by introducing a transgene comprising the VEGF gene, an angiogenic gene, operably linked to the bovine rhodopsin promoter (page 282, paragraph bridging columns 1-2; page 282, column 2, *Generation of Transgenic Animals*) which drives expression of VEGF to the retina, causes neovascularization of the eye. Okamoto did not teach viral gene delivery to make the animal model.

In particular, at the time that the claimed invention was made, viral-mediated gene delivery to the retina of an animal was within the routine skill level of the ordinary artisan. Rokoczy taught the use of gene delivery vectors to introduce heterologous genes to the retina. Rokoczy taught using both AV and AAV vector to introduce gene expression to the retina (page 279, column 1) via subretinal injection (page 279, column 2, paragraph 2). Tomidokoro taught

the utility of using one eye of an animal as a treated, experimental sample while using the other eye as an experimental control (page 382, column2, lines 44-47).

Accordingly, at the time the claimed invention was made, it would have been obvious for one of skill in the art at the time the invention was made, to generate a model of ocular neovascularization in a mouse by delivering the VEGF gene taught by Okamoto according to the method of viral gene delivery of Rakoczy. One of ordinary skill in the art would have been sufficiently motivated to use the VEGF gene with the method of Rakoczy because it was taught by Okomoto that expression of VEGF in the retina leads to neovascularization (Abstract, last sentence; page 282, column 2, lines 1-3). In particular, one of ordinary skill in the art would have been motivated to use virus-mediated gene delivery to generate an animal model over the transgenic techniques of Okamoto because the gene-delivery model would have the utility of providing both experimental and control systems as the animal would have two genetically identical eyes that can be manipulated independently (refer to Tomidokoro, specifically page 382, column 2, lines 44-47). Accordingly, one eye can be used to generate a model of neovascularization using the claimed methods while the other can be used as a control.

Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632

Application No.: 10/090983

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: All nucleic acid sequences in the spec require SEQ ID NOs. For example, see page 34, lines 8-9.

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE